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IMPACT OF CALCIUM-CHANNEL BLOCKERS ON RIGHT HEART FUNCTION IN A CONTROLLED MODEL OF CHRONIC PULMONARY HYPERTENSION

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Abstract

Purpose—Patients with chronic pulmonary hypertension (CPH) who demonstrate a pulmonary vasodilation following calcium channel blocker (CCB) administration are defined as “responders”. In contrast, “non-responders” are patients who do not show such a pulmonary vasodilation with CCB therapy. The purpose of this investigation was to study the effects of CCB therapy on right heart mechanics in experimental CCB responders versus CCB non-responders.

Methods—In 12 dogs, right atrial (RA) and ventricular (RV) pressure and volume (conductance catheters) were simultaneously recorded after 3 months of progressive pulmonary artery (PA) banding. Diltiazem was given at 10 mg/hr with the PA constricted (simulated CCB non-responder). Responders were then created by releasing the PA band to unload the ventricle. RA and RV contractility and diastolic stiffness (slope of end-systolic and end-diastolic pressure-volume relations) were calculated and RA reservoir and conduit function were quantified as RA inflow with the tricuspid valve closed versus open, respectively.

Results—With CCB, RA contractility ($p < 0.03$) and cardiac output ($p < 0.004$) were compromised in simulated non-responders while RA stroke work was pharmacologically depressed in the setting of an unchanged afterload. After simulating a responder by controlled PA band release, the RA became less distensible, causing a shift from reservoir to conduit function ($p < 0.001$) towards physiologic baseline conditions and a recovery in the hyperdynamic compensatory response in both chambers ($p < 0.007$) as evidenced in a declined RA and RV contractility with an improved cardiac output as compared to CPH and simulated non-responders. RA and RV diastolic function in both groups was not affected by CCB.

Conclusions—CCB did not impact RV function in simulated non-responders, but significantly impaired RA contractility and cardiac output. In simulated responders, afterload fell substantially,

thereby allowing the RA and RV to recover from their pathological hyperdynamic contractile response to CPH. This affect was able to outweigh the intrinsic negative effects of CCB therapy on systolic RA function. Current data suggest that the RA in CPH is much more sensitive to CCB therapy than the RV and delineate for the first time why CCB therapy in CPH has been empirically restricted to documented responders.

Keywords

calcium-channel blockers; chronic pulmonary hypertension; right heart function

Introduction

Historically, calcium-channel blockers (CCB) have been considered the mainstay therapy, and first line agent for conventional medical management of primary pulmonary hypertension (PPH). However, side-effects including hemodynamic deterioration in some patients, have discouraged the initial enthusiasm for the use of CCB.^{1–4} Unpredictable clinical results have led to a paradigm shift towards more restricted use of CCB in recent years. Although the risk of acute hemodynamic impairment may be reduced by using inhaled nitric oxide, adenosine, or intravenous epoprostenol, the appropriate patient selection for this therapeutic approach remains controversial.^{3,4}

Patients who could potentially benefit from long-term treatment may be identified by acute vasodilator challenge.^{5,6} In “responders”, a 20% decrease in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) occurs following CCB administration. The reported percentage of patients who turn out to be clinical and hemodynamic long-term responders to CCB treatment is 10–15%.⁷ While multiple animal studies have demonstrated the beneficial vasodilatory effect of CCB on the pulmonary vascular bed in various models of pulmonary hypertension,^{8–10} their complex interactions with right atrial (RA) and right ventricular (RV) function have yet to be examined. Specifically, concern exists that CCB therapy in patients who do not demonstrate a decrease in PAP and PVR following CCB administration (“non-responders”) may further impair cardiac function. However, the detailed effects of CCB on right heart mechanics in responders versus non-responders remain unknown. While successful treatment with CCB is restricted to a subgroup of patients, it was recently shown still to be an extremely powerful therapeutic option in long-term responders (5 year survival 97% vs. 58% in non-responders, $p=0.0007$).⁴ Therefore, the purpose of the current investigation was to determine the balance between afterload reduction, changes in diastolic relaxation and compliance, and contractile inhibition in an experimental canine CPH model of CCB responders and non-responders.

Methods

Initial Surgical Preparation

Twelve adult mongrel dogs of either sex (20–25 kg) underwent a median sternotomy, leaving the pericardium intact. A 5-Fr pressure catheter (Access Technologies, Skokie, IL) was introduced into the RV free wall through a pursestring suture and secured in place. An inflatable silastic band (16 mm diameter, Access Technologies, Skokie, IL) was secured around the distal main pulmonary artery (PA). The PA band and RV pressure (RVP) catheter were tunneled through the left and right lateral chest walls, respectively, and connected to small ports that allowed injection of saline and pressure monitoring.¹¹

Creation of Chronic RV Pressure Overload

Approximately one week after the initial operation, when the animal was fully recovered, RV pressure overload was initiated in a stepwise manner with progressive inflation of the PA band. Inflation of the PA band was performed weekly, increasing RVP by 10 to 20 mmHg at each inflation until near systemic pressures were achieved.¹²

Data Acquisition after Creation of Chronic RV Pressure Overload

Animals underwent a second study an average of 112 ± 54 days after the initial baseline study. Ultrasonic flow probes (10–12-mm perivascular probes with a T206 Flowmeter, Transonic Systems; Ithaca, NY) were placed around the superior (SVC) and inferior (IVC) vena cava approximately 1 cm from the caval-atrial junction to measure RA inflow. A 1 cm mini-pericardiotomy was performed over the anterior RV free wall, and a 6-Fr combined pressure-volume (PV) conductance catheter (Millar SPR-843) was introduced through a pursestring suture just below the pulmonary valve and positioned towards the RV apex.¹² A second 1 cm incision was made in the pericardium over the RA appendage, and a 5-Fr combined PV conductance catheter (Millar SPR-766) was positioned along the long axis of the right atrium so that its tip rested at the RA-IVC junction.^{11,12,13} The RA and RV PV catheters were connected to two signal conditioner processors (Sigma 5DF, CD Leycom; Zoetermeer, The Netherlands).¹⁴

Data Acquisition

Baseline data were recorded during steady-state conditions with the PA band inflated to simulate conditions as they appear during chronic pulmonary hypertension (CPH). During each data acquisition run, ECG, RAP, RVP, aortic pressure, SVC flow, IVC flow, and RA and RV conductance signals were acquired at 200 Hz and processed using custom-designed computer software. After steady-state data were obtained (3 to 5 beats), slow, progressive vena caval occlusion was performed to generate RA and RV PV loops over a wide physiologic range of filling pressures.

After baseline data were collected, intravenous administration of Diltiazem 10mg/hr (Diltiazem Hydrochloride, Novaplus, Bedford, OH) was initiated. Following a 20-minute stabilization period, data were collected with the PA band still inflated to simulate a CCB non-responder. Finally, the PA cuff was released in order to unload the right ventricle, (thereby simulating a CCB responder), and standardized data collection was repeated. According to the clinical definition of a CCB responder we released the PA band until a decline in 20%–30% of mean PA and RV pressure was monitored.

At the conclusion of the experiment, the animals were euthanized using sodium pentothal (1 g IV) followed by potassium chloride (80 meq IV), and proper positioning of the catheters was confirmed. All animals received humane care in compliance with the “Principles of Laboratory Animal Care” formulated by the National Society for Medical Research and the “Guide for the Care and Use of Laboratory Animals” prepared by the National Academy of Sciences and published by the National Institutes of Health. The study was approved by the Washington University School of Medicine Animal Studies Committee and conducted according to Washington University policy. The authors have chosen to stick to the well established chronic canine model for the purpose of this study since the complex instrumentation necessary to simultaneously assess RV and RA biomechanics at different levels of RV afterload currently precludes the use of a rodent-model.

Data Analysis

RA elastance (contractility) was calculated using the the “right atrial end-systolic” pressure-volume relationship (RA-ESPVR, chamber elastance) as previously described in detail.^{12, 15} Similarly, static RA stiffness was defined as the slope of the “right atrial end-diastolic” pressure-volume relationship (RA-EDPVR).

RV elastance and stiffness—Similar mathematical methods were used to calculate RV elastance and stiffness as the slope of the RV-ESPVR and RV-EDPVR.^{16,17}

Right ventricular-arterial coupling

Effective arterial elastance (RV E_a) of the pulmonary vascular bed estimates RV afterload and is a function of end-systolic RVP and stroke volume (SV): $E_a = RVP_{ES} / SV$.¹⁷ Effective arterial elastance represents a steady-state approximation of maximum pulmonary vascular impedance. The right ventricular-arterial coupling ratio, E_a / E_{ES} , was then computed, which reflects the elastance matching status between the right ventricle and the pulmonary arterial load in the pressure-volume framework. For the ventricle, stroke work is maximal when arterial elastance equals ventricular elastance ($E_a / E_{ES} = 1$); however, pump efficiency is maximized when arterial elastance is one-half the ventricular elastance ($E_a / E_{ES} = 0.5$).¹⁷

RA stroke work—As previously described for the left atrium,¹⁸ right atrial A and V pressure-volume loop areas (Figure 1) were calculated during the three different hemodynamic states in our study (CPH, CCB non-responder, CCB responder). Net mechanical work by the right atrium was computed by subtracting the V loop area from the A loop area.¹⁹ Custom-designed software was used to identify the PV crossover point between the A and V loop area.

RA reservoir and conduit function—Reservoir and conduit function of the right atrium were calculated by integrating RA inflow (combined SVC and IVC flow) during RV systole (reservoir) and RV diastole (conduit).^{12,13,20,21}

Statistics

All data are reported as mean $\pm$ SD. Hemodynamic data obtained during steady-state recording are reported as the average of three consecutive beats. Data were recorded with chronic PA banding (CPH) and after subsequent administration of Diltiazem 10mg/hr with the PA band still constricted (CCB non-responder) and released (CCB responder). The data were compared between the three states using repeated-measures analysis of variance (ANOVA). Using power analysis, the number of animals studied ($n = 12$) was selected to yield an 80% power of detecting a one standard deviation difference between various physiologic states ($\alpha = 0.05$). All statistical analyses were performed using SigmaStat 2.03 (SPSS Inc., Chicago, IL). To control for data that were not evenly distributed, we performed normality testing for each paired statistical test prior to selecting a parametric vs. non-parametric comparison.

Results

Figure 2 illustrates typical hemodynamic changes from one animal and Table 1 summarizes the steady-state hemodynamic data at CPH (chronic PA banding), after CCB administration in simulated CCB non-responders (persistent PAP elevation), and in simulated CCB responders (PA band release).

Overall, with CCB, RV elastance (contractility) did not significantly change in CCB non-responders, but decreased in CCB responders from 15.0 ± 11.3 mmHg/ml at baseline to 5.7 ± 3.0 mmHg/ml ($p=0.007$), associated with a reduction in RV V_0 (volume-axis intercept of the

slope of the ESPVR) ($p=0.004$). There was no change in RV stiffness ($p=0.58$) and RV V_{ED} (volume-axis intercept of the slope of the EDPVR) ($p=0.93$) in CCB non-responders (Table 2). Although there was a significant decline in RV elastance in CCB responders, there was a simultaneous decline in RV afterload (E_a) ($p<0.001$), resulting in no significant change in the ventricular-arterial coupling ratio (E_a / E_{ES}) ($p=0.12$).

CCB administration caused RA elastance to fall from 1.8 ± 0.9 mmHg/ml at baseline to 1.5 ± 0.6 mmHg/ml in CCB non-responders ($p=0.03$) and 0.9 ± 0.4 in CCB responders ($p<0.001$ vs. baseline). There was no significant change in RA V_0 with either intervention ($p=0.85$). Like the ventricle, there was also no significant change in RA EDPVR with either intervention ($p=0.84$ stiffness, $p=0.92$ intercept) (Table 3).

Net RA mechanical work (A loop area minus V loop area) significantly dropped from CPH (1.8 ± 1.6) to CCB non-responders (0.8 ± 1.0 , $p=0.02$) and further declined in simulated CCB responders (0.0 ± 0.9 , $p<0.001$) (Table 4).

At CPH, reservoir function accounted for $68\% \pm 21\%$ of RA inflow (12 ± 4 mL) and conduit function for $32 \pm 27\%$ (5 ± 2 mL). With CCB administration there was no change in reservoir ($68 \pm 13\%$, 10 ± 1 mL) versus conduit ($32 \pm 13\%$, 4 ± 2 mL) function in CCB non-responders ($p=0.38$). However, in CCB responders, the RA became less distensible, evidenced by a shift from reservoir ($53 \pm 18\%$, 7 ± 3 mL) to conduit ($47 \pm 18\%$, 7 ± 3 mL) function ($p<0.001$).

Discussion

The results of this study demonstrated the complexity of the interplay between the right atrium and right ventricle in a state of chronic pressure overload. With CCB, RA contractility and cardiac output were significantly compromised in simulated non-responders while RA stroke work was pharmacologically depressed in the setting of an unchanged afterload. After simulating a responder by controlled PA band release, the RA became less distensible, causing a shift from reservoir to conduit function towards physiologic baseline conditions and a recovery in the hyperdynamic compensatory response in both chambers as evidenced in a declined RA and RV contractility with an improved cardiac output as compared to CPH and simulated non-responders.

Current findings showed for the first time that CCB therapy in simulated non-responders impaired RA contractility in the setting of persistently elevated RV afterload, thereby impacting right heart throughput in a negative way. Prior to any manipulation, Hoit and colleagues demonstrated in control dogs that A and V loop pressure-volume areas from the left atrium were similar in size.¹⁸ Consequently, the net left atrial work (A loop area minus V loop area) was not significantly different from zero. In our study of right heart mechanics, in the setting of chronic pressure overload, RA A loop area was five-fold higher than V loop area, consistent with increased RA work, potentially due to a physiologic hyperdynamic response. With Diltiazem administration in simulated non-responders, RA work decreased ($p<0.001$). Intuitively, this appears counterproductive; in the presence of persistent RV pressure overload, increased RA work would be necessary to maintain RV filling and cardiac output. Thus, pharmacological depression with CCB administration in simulated non-responders produced an undesirable fall in cardiac output. Compromised RA contractility and RA stroke work in simulated non-responders seems particularly disturbing since previous work from our laboratory suggested that RA function plays an increased role in maintaining RV output when the ventricle begins to fail.^{12,22,23} Interestingly, RV function was not altered by CCB in simulated non-responders.

It has been well described that CCB reduce the amount of sarcoplasmic reticular Ca^{++} release, which results in myofilament cross-bridge formation and subsequent myocyte contraction.²⁴

Therefore, we could have expected CCB to impair RV contractility, as previous studies have demonstrated in isolated myocytes.^{24,25} However, other investigators have shown that the RV compensatory response to chronic pressure overload is one of increased contractility at the expense of impaired diastolic function due to myocardial hypertrophy and subsequent remodeling.^{12,26,27} While mild myocardial hypertrophy does not appear to affect L-type Ca^{++} channel abundance and function, the development of moderate-to-severe hypertrophy has been associated with diminished Ca^{++} channel density and activity.²⁴ In rats chronically exposed to hypobaric conditions, Chouabe and coworkers reported that the development of right ventricular hypertrophy was associated with a 27% reduction in L-type Ca^{++} abundance.²⁸ In the current study, we did not quantify the degree of RV or RA hypertrophy, and histological evaluation of the right atrium and ventricle was not performed. However, in a similar preparation, Hsieh and colleagues induced pulmonary hypertension in dogs and found moderate-to-severe myocyte hypertrophy in the RV outflow tract compared to only mild hypertrophy within the atrium.²⁹

To simulate CCB responders, the PA band was released, which acutely unloaded the right heart. Heart rate fell by 16% compared to baseline, and RV contractility decreased substantially, characterized by a decrease in RV ESPVR and RV dP/dt, consequent to the 37% fall in RVP. These findings are consistent with reversal of the normal hyperdynamic response of the right ventricle to CPH.¹¹ The substantial fall in afterload enabled the heart to augment cardiac output despite a decline in the RA and RV hyperdynamic contractile response. Thus, both the slower heart rate and the diminished RV and RA contractility can be interpreted as a beneficial recovery which made the RA and RV work more economic as compared to CCB non-responders. With diminished RV afterload, the further decline in RA work can also be judged as a beneficial effect.

After PA band release in the current study, the right atrium became less distensible, causing a shift from RA reservoir to conduit function. In a previous report from our laboratory, Gaynor and associates identified a substantial rise in reservoir function from 49% to 72% with chronic RV pressure overload, consistent with the increase in atrial distensibility that previous investigators predicted would have a positive impact on cardiac output.^{20,30,31} By creating a CCB responder, we eliminated the cause of the RA shift towards augmented distensibility, with reservoir function falling back to its normal physiologic range.¹²

It is well accepted that myocardial relaxation is highly dependent upon calcium flux, and that relaxation occurs as the sarcoplasmic reticulum reaccumulates free ionized calcium, causing it to dissociate from troponin C. Interestingly, bi-chamber stiffness, quantified using the RA and RV EDPVR, did not substantially fall in CCB non-responders nor CCB responders. As described above, the effects of CCB are dependent on L-type Ca^{++} channel density and are, therefore, likely to be diminished in hypertrophic RV myocardium. Down-regulation of calcium-handling proteins, including sarcoplasmic reticulum Ca^{++} -ATPase2a (SERCA2a) and phospholamban (PLB), has been described in the failing heart.³² These proteins are important regulators of intracellular calcium homeostasis and have been implicated in myocardial dysfunction; reduction in these proteins is associated with increased calcium transient times. Despite only mild morphological changes within the right atrium, these findings may, in part, explain why there were no changes in bi-chamber EDPVR in the current report; however, further investigations will be necessary to delineate the molecular mechanisms responsible for these findings.

In summary, CCB did not alter RV function in simulated non-responders but significantly impaired RA function culminating in a decline in cardiac output. In simulated CCB responders, afterload fell dramatically to improve cardiac output despite a reversal of the pathological hyperdynamic RA and RV contractile response to CPH. This mechanism may explain

favorable long-term results observed in clinical CCB responders. In the clinical setting, such RV afterload reduction is dependent on pulmonary vasodilation. Thus, the current study also suggests that once vascular hypertrophy and remodeling of the smooth muscle cells prevents reversal of pulmonary vasoreactivity (CCB non-responders), patients are subject to hemodynamic impairment mainly as a consequence of compromised RA function.

Potential Limitations

Our model of pulmonary artery banding does not perfectly represent a chronic pulmonary hypertension scenario in humans as it is the small vessels that are mainly affected in these patients. Injecting Monocrotaline, an alkaloid known to produce progressive pulmonary hypertension in certain species, is a well described alternative technique but is limited by its ability to only cause a modest rise in RV pressure and was therefore not deemed suitable for the purpose of the current investigation. The same standardized study protocol used for this report has also served for a previous study from our laboratory at Washington University in St. Louis, School of Medicine.¹² Using the same chronic instrumentation, RA and RV pressure and volume were recorded at baseline and after 3 months of progressive pulmonary artery banding. RV elastance and stiffness both increased ($P<0.05$), suggesting preserved RV systolic function but impaired RV diastolic function (decreased RV compliance). In another previous chronic canine study using the similar instrumentation RV hypertrophy in response to chronic pulmonary artery banding has been demonstrated.²⁹ While we did perform echocardiography periodically to monitor the development of RV dilation and CPH, we did not specifically quantify RV hypertrophy and did not store the echo images to allow later reevaluation. We did perform MRI studies on three dogs as a pilot study in which we did see thickened RV wall, but these data remain anecdotal. Although RA conductance volume was not corrected for parallel conductance (resistance to current due to surrounding tissues), the analytic methods employed in this study were not dependent on absolute volume measurements and were consistent with previous studies involving the right atrium.¹¹ The shorter time period as compared to the clinical setting of CPH is another shortcoming of the current chronic canine model. However, the study endpoint was defined as the development of clinical signs of right heart failure which typically developed after 3 months of progressive PA banding.

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FIGURE 1.

Typical examples of two right atrial pressure-volume loops, recorded after three month of progressive pulmonary artery banding (CPH; dotted loop) and in a simulated calcium channel blocker (CCB) non-responder (solid loop). Net right atrial mechanical work was calculated by subtracting the V loop area (V) from the A loop area (A). In this dog, right atrial mechanical work (A minus V loop area) was substantially higher at CPH as compared to the simulated CCB non-responder.

FIGURE 2.

Typical hemodynamic data obtained with calcium channel blocker (CCB) administration in simulated CCB non-responders and CCB responders after 3 months of progressive pulmonary artery banding (CPH). Three steady-state beats of the right ventricle (black line) and right atrium (gray line) are illustrated for each hemodynamic state.

TABLE 1

Hemodynamic effects with calcium channel blocker (CCB) administration in simulated CCB non-responders versus CCB responders with chronic pulmonary artery banding (CPH) (n=12).

	CPH	CCB Non-Responder	CCB Responder
Heart rate (beats/min)	126 ± 23	113 ± 24 [*]	106 ± 25 [*]
Mean aortic pressure (mmHg)	72 ± 23	72 ± 30	66 ± 26 [*]
Maximum RV pressure (mmHg)	60 ± 19	62 ± 20	39 ± 14 [*]
Mean RA pressure (mmHg)	7 ± 3	6 ± 2	6 ± 2
Maximum RV volume (mL)	20 ± 6	19 ± 7	19 ± 7
Maximum RA volume (mL)	15 ± 5	15 ± 5	14 ± 5
Maximum RV dP/dt (mmHg/s)	881 ± 566	781 ± 429	579 ± 332 [*]
Maximum RA dP/dt (mmHg/s)	76 ± 27	66 ± 30	62 ± 40
Stroke volume by RA inflow (mL/beat)	17 ± 7	14 ± 9	22 ± 6 ^{*/**}
Cardiac output (L/min)	2.0 ± 0.8	1.6 ± 0.8 [*]	2.4 ± 0.9 [*]

Values are mean ± SD. RA, right atrial; RV, right ventricular.

*
p<0.05 vs. CPH

**
p<0.05 vs. CCB Non-Responder (repeated measures ANOVA).

Table 2

Effects of calcium channel blocker (CCB) administration in simulated CCB non-responders versus CCB responders with chronic pulmonary artery banding (CPH) on right ventricular elastance (contractility), chamber stiffness and ventricular-arterial coupling (n=12).

	CPH	CCB Non-Responder	CCB Responder
R V E_{ES} (mmHg/ml)	15.0 $\pm$ 11.3	13.3 $\pm$ 7.5	5.7 $\pm$ 3.0 *
RV V_0 (ml)	22.2 $\pm$ 16.2	21.2 $\pm$ 16.5	13.4 $\pm$ 7.5 *
Correlation coefficient (r^2)	0.93 $\pm$ 0.04	0.90 $\pm$ 0.15	0.89 $\pm$ 0.11
RV stiffness (mmHg/ml)	1.0 $\pm$ 0.5	1.3 $\pm$ 0.7	1.0 $\pm$ 0.4
RV V_{ED} (ml)	10.2 $\pm$ 6.8	12.3 $\pm$ 6.3	10.3 $\pm$ 7.0
Correlation coefficient (r^2)	0.84 $\pm$ 0.10	0.86 $\pm$ 0.16	0.89 $\pm$ 0.10
RV E_a (mmHg/ml)	12.6 $\pm$ 7.9	13.4 $\pm$ 8.2	5.8 $\pm$ 2.1 *
RV E_a / E_{ES}	0.9 $\pm$ 0.2	1.0 $\pm$ 0.3	1.2 $\pm$ 0.6

Values are mean $\pm$ SD. E_a , effective arterial elastance; E_{ES} , elastance; RV, right ventricular.

* $p < 0.05$ vs. CPH (repeated measures ANOVA).

TABLE 3

Effects of calcium channel blocker (CCB) administration in simulated CCB non-responders versus CCB responders with chronic pulmonary artery banding (CPH) on right atrial elastance (contractility) and chamber stiffness (n=12).

	CPH	CCB Non-Responder	CCB Responder
RA elastance (mmHg/mL)	1.8 ± 0.9	1.5 ± 0.6 *	0.9 ± 0.4 *
RA V ₀ (mL)	9.4 ± 8.1	9.5 ± 5.7	5.5 ± 6.8
Correlation coefficient (r ²)	0.85 ± 0.15	0.92 ± 0.06	0.89 ± 0.07
RA stiffness (mmHg/mL)	1.3 ± 0.6	1.4 ± 0.7	1.3 ± 0.8
RA V _{ED} (mL)	10.0 ± 5.3	10.1 ± 6.0	9.3 ± 5.0
Correlation coefficient (r ²)	0.92 ± 0.07	0.94 ± 0.05	0.90 ± 0.06

Values are mean ± SD. RA, right atrial.

* p<0.05 vs. CPH (repeated measures ANOVA).

TABLE 4

Right atrial A and V pressure-volume loop areas and right atrial work (calculated as A loop area minus V loop area) with chronic pulmonary artery banding (CPH) as well as in simulated calcium channel blocker (CCB) non-responders and responders (n=12).

	CPH	CCB Non-Responder	CCB Responder
A – Loop area	2.2 ± 1.8	1.1 ± 0.9 [*]	0.6 ± 0.9 [*]
V – Loop area	0.4 ± 0.4	0.3 ± 0.2	0.6 ± 0.4
A – Loop minus V – Loop area	1.8 ± 1.6	0.8 ± 1.0 [*]	0.0 ± 0.9 [*]

Values are mean ± SD. RA, right atrial.

* p<0.05 vs. CPH (repeated measures ANOVA).